Comparison of Nedaplatin and Irinotecan for Patients with Squamous and Nonsquamous Cell Carcinoma of the Lung

Meta-Analysis of Four Trials

Fumihiro Oshita, MD, Takeshi Honda, MD, Shuji Murakami, MD, Tetsuro Kondo, MD, Haruhiro Saito, MD, Kazumasa Noda, MD, and Kouzo Yamada, MD

Background: Non-small cell lung cancer has several types of pathology and is moderately responsive to anticancer drugs, but specific chemotherapy regimens for each have not been established.
Methods: We compared the outcomes of patients with squamous and nonsquamous cell carcinoma of the lung, which were compiled from four of our own studies of nedaplatin (NP) with irinotecan (CPT).
Results: One hundred twenty-one patients with stage IIIB/IV non-small cell lung cancer received 50 to 100 mg/m^2 NP and 50 to 60 mg/m^2 CPT per cycle. Eighty-six patients were men and 35 were women, with a median age of 70 years (range, 29–84 years). Seventeen, 88, 8, and 8 patients had a performance status of 0, 1, 2, and 3, respectively. Twenty seven of the 121 patients had squamous cell carcinoma. Responses to the NP and CPT regimen were complete in two cases and partial in 45. The response rate was 51.9 and 35.1% in patients with squamous and nonsquamous cell carcinoma, respectively. Comparisons of survival revealed that the median survival time, 1-year survival rate, and 2-year survival rate were 14.5 and 9.1 months, 63.0 and 39.4%, and 29.6 and 19.1% for patients with squamous and nonsquamous cell carcinoma, respectively.
Conclusions: The NP and CPT regimen is suggested to be more active against squamous cell carcinoma of the lung, and a comparative study to confirm this is recommended.

Key Words: Nedaplatin, Irinotecan, Squamous cell carcinoma, Lung cancer.

(*J Thorac Oncol.* 2011;6: 128–131)

Non-small cell lung cancer (NSCLC) has several types of pathology, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others. All types of NSCLC are moderately responsive to anticancer drugs, and specific chemotherapy regimens for each have not been established. Regimens based on combinations of new anticancer agents such as vinorelbine, gemcitabine, docetaxel, and paclitaxel with platinum compounds have emerged as a gold standard for chemotherapy-naive NSCLC.[1] The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib has been shown to have high efficacy in patients with previously treated advanced NSCLC.[2] Specific missense and deletion mutations in the tyrosine kinase domain of the *EGFR* gene are reportedly associated with sensitivity to gefitinib,[3,4] and patients with NSCLC with EGFR mutation have been retrospectively demonstrated to achieve a better outcome with gefitinib treatment than the patients with the wild-type EGFR.[5] We have also found that patients with EGFR mutation have a significantly higher response rate to gefitinib, and also significantly longer survival, than patients with wild-type EGFR.[6] Currently, therefore, NSCLC with EGFR mutation is an independent pathologic type that is considered to require a specific chemotherapy regimen.

Pemetrexed is a potent inhibitor of thymidylate synthase and other folate-dependent enzymes and is currently approved as a first-line treatment for malignant pleural mesothelioma. A randomized phase III study has shown that a regimen comprising cisplatin and pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin and gemcitabine as a first-line treatment for advanced NSCLC.[7] The study also demonstrated that cisplatin and pemetrexed provided better overall survival in patients with adenocarcinoma and large cell carcinoma. Therefore, these recent studies suggest that uniform treatment for NSCLC may not be appropriate, and that treatment needs to be tailored according to histologic or genetic type.

Nedaplatin (NP) is an analogue of cisplatin, with relatively low neuro- and nephrotoxicity. Three-dimensional analytical models have demonstrated marked synergistic interaction of concurrently administered NP and irinotecan (CPT).[8] A phase I/II study showed high activity and low toxicity of NP and CPT against NSCLC,[9] and some other studies of NP and CPT against advanced NSCLC yielded similar results, together with favorable patient survival.[10–12] No differences in activity among histologic types were evident, but NP was basically active against squamous cell

Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan.
Disclosure: The authors declare no conflicts of interest.
Address for correspondence: Fumihiro Oshita, MD, Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama 241-0815, Japan. E-mail: foshita@kcch.jp

ISSN: 1556-0864/11/0601-0128

carcinoma. Here, we analyze the outcomes of our previously published studies using NP and CPT for chemotherapy-naive patients with NSCLC and compare them between squamous and nonsquamous cell carcinoma.

PATIENTS AND METHODS

We analyzed four studies, (1) phase I/II study of escalating doses of NP in combination with CPT for advanced NSCLC,[9] (2) phase II study of NP and CPT for elderly patients with advanced NSCLC,[10] (3) feasible combination of chemotherapy with NP and CPT for patients with NSCLC and multiple high-risk factors,[11] (4) phase II study of NP and CPT followed by gefitinib for elderly patients with unresectable NSCLC.[12] The Institutional Review Board of Kanagawa Cancer Center reviewed and approved every study analyzed in this investigation.

Patients

Patients with histologically or cytologically proven unresectable NSCLC were registered for each study of NP and CPT. Eligibility criteria for the chemotherapy were absence of any prior chemotherapy and Eastern Cooperative Oncology Group performance status score ≤3. Patients with postoperative recurrence and patients who had received radiotherapy for metastatic lesions were eligible for each study, and at least 4 weeks rest was required after prior surgery or radiation therapy. Written informed consent was obtained in every case.

Chemotherapy

Patients exhibiting no progression of the disease were treated every 4 weeks with CPT on days 1 and 8, and with NP on day 1 only or on days 1 and 8. CPT was used at 50 or 60 mg/m^2 on each day, and NP was used at 50 to 100 mg/m^2 on each day (Table 1). The NP and CPT chemotherapy was repeated for a maximum of four cycles unless the disease progressed or if severe toxicities developed. Tumor responses were evaluated according to the RECIST criteria.[13]

Statistical Analysis

The χ^2 test was used to identify differences between squamous and nonsquamous cell carcinoma. The Kaplan-Meier method was used to estimate the probability of survival, and differences in survival were analyzed by the log-rank test. All analyses were performed using StatView or Fisher's software.

RESULTS

Between April 1997 and January 2006, a total of 139 patients were registered in the four studies. One hundred twenty one of them had clinical stage IIIB or IV disease, and their outcomes were analyzed in this study. Eighty-six patients were men and 35 were women, with a median age of 70 years (range, 29–84 years). Seventeen, 88, 8, and 8 patients had a performance status of 0, 1, 2, and 3, respectively. Twenty-seven patients had squamous cell carcinoma. Twenty-five and 96 patients were at stages IIIB and IV, respectively. Patient characteristics in each group are summarized in Table 2. All patients were assessed for response and survival. Responses to the NP and CPT regimen in the 121 patients were complete in two cases and partial in 45. Both of the patients who achieved a complete response and whose tumors did not recur for 5 years had squamous cell carcinoma. The response rate was 51.9 and 35.1% for patients with squamous and nonsquamous cell carcinoma, respectively. Comparison of survivals among the various pathologic types revealed that the median survival time, 1-year survival rate, and 2-year survival rate were 14.5 and 9.1 months, 63.0 and 39.4%, and 29.6 and 19.1% for squamous and nonsquamous cell carcinoma, respectively (Table 3).

DISCUSSION

NP has been shown to have antitumor activity against squamous cell carcinoma originating from multiple organs such as the lung,[14] esophagus,[15] head and neck,[16] and uterine cervix.[17] Not only CPT but also other drugs such as docetaxel, paclitaxel, and 5-fluorouracil have been combined with NP and demonstrated to have activity against squamous cell carcinoma of these organs.[14–17] Although we were unable to find any differences in treatment outcome between squamous and nonsquamous cell carcinoma in each of the previous studies, the present meta-analysis suggested that NP and CPT elicit favorable responses and survival in patients with squamous cell carcinoma. A randomized phase III study that demonstrated a significant improvement in survival with cisplatin plus pemetrexed in patients with adenocarcinoma suggested that higher baseline expression of the thymidylate synthase gene and protein was related to the difference in survival.[7] It has been suggested that NP is more effective against squamous cell carcinoma than against adenocarcinoma,[18] although the mechanism of sensitivity to NP in lung cancer has not been elucidated. For squamous cell carcinoma, predictors of tumor

TABLE 1. Summary of Studies

Phase	n	NP (mg/m^2/d)	CPT (mg/m^2/d)	Clinical Stage	Age (yr), Median (Range)	Gr. 3/4 Diarrea (%)	Gr. 4 Neut. (%)	FN (%)	RR (%)	MST (mo)	1-yr Surv (%)	Reference
I/II	42	50–100 (day 1)	60 (days 1, 8)	IIIA-IV	55 (29–69)	1.0	9.3	12.4	31.0	11.4	45.2	9
II	38	100 (day 1)	60 (days 1, 8)	IIB-IV	74 (71–84)	7.9	50.0	26.3	65.8	13.9	55.3	10
II	28	50 (days 1, 8)	60 (days 1, 8)	IIIB/IV	74 (70–81)	1.4	33.8	4.2	39.3	8.7	42.9	12
Pilot	31	50 (days 1, 8)	50 (days 1, 8)	IB-IV	63 (30–86)	0	8.4	13.3	45.2	7.7 (IIIB/IV)	38.5 (IIIB/IV)	11

We deleted 18 patients with stage IB to IIIA and analyzed patients with stage IIIB or IV.
NP, nedaplatin; CPT, irinotacan; gr., grade; neut., neutropenia; FN, febrile neutropenia; RR, response rate; MST, median survival rate; 1-yr surv, 1-yr survival rate.

TABLE 2. Patient Characteristics

	Nonsquamous (n = 94)		Squamous (n = 27)		
	No. of Patients	%	No. of Patients	%	*p*
Age (yr)					
Median	71		65		0.747
Range	29–84		42–81		
Gender					
Male	60	63.8	26	96.3	0.002
Female	34	36.2	1	3.7	
PS (ECOG)					
0	16	17.0	1	3.7	0.188
1	68	72.3	20	74.1	
2	5	5.3	3	11.1	
3	5	5.3	3	11.1	
Stage					
IIIB	13	13.8	12	44.4	0.001
IV	81	86.2	15	55.6	

PS, performance status; ECOG, Eastern Cooperative Oncology Group.

TABLE 3. Comparison of Outcomes Between Squamous and Nonsquamous Cell Carcinoma after Treatment with Nedaplatin and Irinotecan

	Nonsquamous	Squamous	*p*
Cases	94	27	
Response rate (%)	35.1	51.9	0.115
MST (mo)	9.1	14.5	0.127
1-yr surv. (%)	39.4	63.0	0.023
2-yr surv. (%)	19.1	29.6	0.243

MST, median survival time; surv., survival rate.

response to chemotherapy have been investigated in other organs, from which samples of tumor tissue can be easily obtained for analysis of genetic expression. Expression of Her-2 and EGFR in tumor tissue has been shown to be a potentially reliable predictive indicator of sensitivity to cisplatin in head and neck squamous cell cancer.[19] Another study has revealed that tumors with p53 mutation are more common among nonresponders to neoadjuvant chemotherapy in patients with head and neck squamous cell carcinoma.[20] Repair-related genes, such as *ERCC-1* or *XRCC1*, are known to be good predictors of chemotherapeutic response in esophageal squamous cell carcinoma.[21,22] Chemosensitivity of squamous cell carcinoma of the lung had not been analyzed because of the low availability of tumor tissues for gene analysis in patients with unresected advanced NSCLC. We have suggested that DNA damage in peripheral blood mononuclear cells can be predictive of response to cisplatin-based chemotherapy.[23] It suggest that DNA from peripheral blood cells or cancer tissue may be available for analysis of genetic predictors of chemosensitivity, and we anticipate the emergence of a reliable biomarker for prediction of sensitivity to NP.

CONCLUSIONS

NP and CPT is suggested to be more effective against squamous cell carcinoma than against nonsquamous cell carcinoma, and a large comparative study to confirm this seems warranted.

ACKNOWLEDGMENT

Supported in part by Kanagawa Health Foundation and Kanagawa Prefectural Hospitals Cancer Research Fund.

REFERENCES

1. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
2. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *J Clin Oncol* 2003;21: 2237–2246.
3. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
4. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304: 1497–1500.
5. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005;23:2513–2520.
6. Oshita F, Matsukuma S, Yoshihara M, et al. Novel heteroduplex method using small cytology specimens with a remarkably high success rate for analysing EGFR gene mutations with a significant correlation to gefitinib efficacy in non-small-cell lung cancer. *Br J Cancer* 2006;95: 1070–1075.
7. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
8. Kanzawa F, Koizumi F, Koh Y, et al. In vitro synergistic interactions between the cisplatin analogue nedaplatin and the DNA topoisomerase I inhibitor irinotecan and the mechanism of this action. *Clin Cancer Res* 2001;7:202–209.
9. Oshita F, Yamada K, Kato Y, et al. Phase I/II study of escalating doses of nedaplatin in combination with irinotecan for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003;52:73–78.
10. Oshita F, Yamada K, Saito H, et al. Phase II study of nedaplatin and irinotecan for elderly patients with advanced non-small-cell lung cancer. *J Exp Ther Oncol* 2004;4:343–348.
11. Oshita F, Saito H, Yamada K. Feasible combination chemotherapy with nedaplatin and irinotecan for patients with non-small cell lung cancer and multiple high-risk factors. *J Exp Ther Oncol* 2007;6:251–256.
12. Oshita F, Yamada K, Saito H, et al. Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2008;62: 465–470.
13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
14. Okuda K, Hirose T, Ishida H, et al. Phase I study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2008;61:829–835.
15. Gong Y, Ren L, Zhou L, et al. Phase II evaluation of nedaplatin and paclitaxel in patients with metastatic esophageal carcinoma. *Cancer Chemother Pharmacol* 2009;64:327–333.
16. Fuwa N, Kodaira T, Tachibana H, et al. Dose escalation study of nedaplatin with 5-fluorouracil in combination with alternating radiotherapy in patients with head and neck cancer. *Jpn J Clin Oncol* 2007;37: 161–167.

17. Watanabe Y, Nakai H, Etoh T, et al. Feasibility study of docetaxel and nedaplatin for recurrent squamous cell carcinoma of the uterine cervix. *Anticancer Res* 2008;28:2385–2388.
18. Fukuda M, Shinkai T, Eguchi K, et al. Phase II study of (glycolate-*O*,*O*′) diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. *Cancer Chemother Pharmacol* 1990;26:393–396.
19. Hasegawa Y, Goto M, Hanai N, et al. Prediction of chemosensitivity using multigene analysis in head and neck squamous cell carcinoma. *Oncology* 2007;73:104–111.
20. Cabelguenne A, Blons H, de Waziers I, et al. p53 alterations predict tumor response to neoadjuvant chemotherapy in head and neck squamous cell carcinoma: a prospective series. *J Clin Oncol* 2000;18:1465–1473.
21. Wu X, Gu J, Wu TT, et al. Genetic variations in radiation and chemotherapy drug action pathways predict clinical outcomes in esophageal cancer. *J Clin Oncol* 2006;24:3789–3798.
22. Warnecke-Eberz U, Metzger R, Miyazono F, et al. High specificity of quantitative excision repair cross-complementing 1 messenger RNA expression for prediction of minor histopathological response to neoadjuvant radiochemotherapy in esophageal cancer. *Clin Cancer Res* 2004; 10:3794–3799.
23. Oshita F, Yamamoto N, Fukuda M, et al. Correlation of therapeutic outcome in non-small cell lung cancer and DNA damage assayed by polymerase chain reaction in leukocytes damaged in vitro. *Cancer Res* 1995;55:2334–2337.

